

REMARKS

Entry of the foregoing, reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

I. Claim Amendments

By the foregoing amendments to the claims, claims 10, and 13-19 have been amended, and claims 2, 3, 11, 12, and 20 have been canceled.

In particular, the claims have been amended to recite a particular ratio of manganese to promoter (i.e. from 2:1 to 3:1).

Additional amendments to the claims have also been made to clarify the claim language, for consistency, and to bring the claims into better conformance with U.S. patent practice (e.g. replacing the phrase "*A* composition according to claim . . ." with the phrase "*The* composition according to claim . . .). These amendments are merely editorial in nature and are not intended to change the scope of the claims or any elements recited therein.

The amendments to the claims, including cancellation of claims, have been made without prejudice or disclaimer to any subject matter recited or canceled herein. Applicants reserve the right to file one or more continuation and/or divisional applications directed to any canceled subject matter. No new matter has been added, and entry of the foregoing amendments to the above-identified application are respectfully requested.

II. Response to Claim Rejections Under 35 U.S.C. § 102

A. At pages 2-3 of the Office Action, claims 2, 4-11, 13-18, 21, and 22 have been rejected under 35 U.S.C. § 102(b) as purportedly being anticipated by Pettersson et al. (International Publication No. WO 98/11922).

B. At pages 3-4 of the Office Action, claims 2, 4-11, 13-19, 21, and 22 have been rejected under 35 U.S.C. § 102(b) as purportedly being anticipated by Thomsen (U.S. Patent No. 6,015,545).

To expedite prosecution in the present application, and not to acquiesce to the Examiner's rejection, the claims have been amended as set forth above. In particular, the claims have been amended to include the subject matter of claims 3, 12, and 20 (reciting a 2:1 to 3:1 ratio of manganese to promoter). Claims 3, 12, and 20 were not included in the

anticipation rejections under 35 U.S.C. § 102. Accordingly, the present amendments should be sufficient to overcome the § 102 rejections, and Applicants respectfully request reconsideration and withdrawal of the same.

III. Response to Claim Rejections Under 35 U.S.C. § 103

At pages 4-5 of the Office Action, claims 2-22 have been rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Pettersson et al. and Thomsen.

This rejection is respectfully traversed, for at least the following reasons.

As noted above, to expedite prosecution in the present application, and not to acquiesce to the Examiner's rejection, the claims have been amended to recite a 2:1 to 3:1 ratio of manganese to promoter. Applicants submit that the subject matter of the present claims is not taught or suggested by Pettersson et al. and Thomsen.

The present claims are directed to contrast medium compositions comprising a physiologically acceptable manganese (Mn) compound and an uptake promoter, and methods for using the same. The claimed compositions provide improved magnetic resonance imaging (MRI) of the liver. In particular, the present inventors have surprisingly found that using ratios of Mn to promoter that are higher than those at which coordination compounds are formed leads to a higher concentration in the liver and thus improved imaging capabilities.

The advantageous properties of the claimed range are verified by the results displayed in Tables 2a, 2b and 3, set forth in the present specification. In these experiments, alanine was used as the uptake promoter. Applicants note that the results displayed in Tables 2a and 2b originate from a different set of animals than the results displayed in Table 3. Therefore, a direct quantitative comparison of Liver Mean Mn content between the Tables is not feasible. Accordingly, the results displayed in the above-mentioned Tables are discussed separately below.

Tables 2a and 2b

Table 2a and 2b (same data but differently grouped) display the Liver Mean Mn (nmol/g) for eleven groups of rats that have been treated with different amounts of Mn, alanine and vitamin D₃. The latter was added in these examples in order to mimic a real clinical situation, where vitamin D₃ is added as a "back-up" uptake promoter to ensure that at least some imaging with Magnetic Resonance Imaging (MRI) is possible. This is discussed

in the specification at page 6, lines 28-31. In Table 2b the results are grouped according to the vitamin D₃ content.

Groups 9, 10 and 11 had a Mn:alanine ratio of 1:0.375 (i.e. 2.67:1), which is representative of the claimed Mn:promoter range of from 2:1 to 3:1. Groups 3-5 and 6-8 had Mn:alanine ratios of 1:1.5 (i.e. 0.67:1) and 1:0.75 (i.e. 1.33:1), respectively, which both fall below the claimed Mn:promoter range.

Group 9 displayed a Liver Mean Mn content of 72.6 nmol/g, which was superior to the contents of groups 3 and 6, which only displayed Liver Mean Mn contents of 69.9 and 69.2 nmol/g, respectively. Group 10 displayed a Liver Mean Mn content of 79.8 nmol/g, which was superior to the contents of groups 4 and 7, which only displayed Liver Mean Mn contents of 72.7 and 73.8 nmol/g, respectively. Group 11 displayed a Liver Mean Mn content of 73.1 nmol/g, which was superior to the contents of groups 5 and 8, which only displayed Liver Mean Mn contents of 68.4 and 72.0 nmol/g, respectively.

Considering each vitamin D3 level (20, 10 or 5 IU/kg body weight) separately, the results in Tables 2a and 2b clearly demonstrate that a molar ratio of Mn:alanine in the range of from 2:1 to 3:1 results in a higher Liver Mean Mn content compared to a Mn:alanine ratio lower than the claimed range.

Table 3

Table 3 displays the Liver Mean Mn (nmol/g) for eight groups of rats that have been treated with different amounts of Mn, alanine and vitamin D₃.

Groups 3 and 4, which had a Mn:alanine ratio of 1:2 (i.e. 0.5:1), below the claimed Mn:promoter range, displayed a Liver Mean Mn of 95.3 and 110.3 nmol/g, respectively. In group 5, the alanine content was decreased so that the Mn:alanine ratio was 1:0.5 (i.e. 2:1). Hence, group 5 was treated with a composition representative of the claimed Mn:promoter range and displayed a Liver Mean Mn of 128.8 nmol/g. In group 6, the alanine content was further decreased so that the Mn:alanine ratio was 1:0.25 (i.e. 4:1), above the claimed range. Group 6 displayed a Liver Mean Mn of 115.9 nmol/g, which was thus lower than group 5.

Also, group 7 was treated with a composition representative of the claimed Mn:promotor range, 1:0.5 (i.e. 2:1) and displayed a Liver Mean Mn of 133.8 nmol/g. In group 8, the composition had a Mn:alanine ratio of 1:0.25 (i.e. 4:1) that was above the claimed range. Group 8 displayed a Liver Mean Mn of 117.8 nmol/g, which was thus lower than that of group 7.

The results in Table 3 demonstrate that the Liver Mean Mn content is highest when a composition in the claimed Mn:alanine range is used, and that it decreases when using a Mn:alanine ratio that is below or above the claimed range.

Importance of small Liver Mean Mn differences

The quantitative differences in Liver Mean Mn content when using a composition in the claimed Mn:promoter range compared to when using a composition outside the claimed range may occasionally appear small as set forth in the above-mentioned Tables. However, relatively small increases in the amount of contrast medium present in examined samples are extremely important in MRI, due to the high sensitivity of the MRI camera. Consequently, any increase of the Liver Mean Mn content improves the signal intensity during MRI which will in turn enhance the image obtained. Thus, even small quantitative differences in the amount of Mn present in the liver gives rise to large qualitative and diagnostic differences.

Information in the cited art

Pettersson et al. relates to the use of manganese and promoters, such as amino acids, for diagnosis of the liver. The Mn:promotor ratio described in the reference is from 1:0.2 (i.e. 5:1) to 1:50 (i.e. 0.02:1). On page 9 of Pettersson et al., it is stated that the preferred molar ratio of manganese to uptake promoter is especially 1:2 to 1:6 and "*particular preferably about 1:5*", i.e. it is preferred to use a Mn:promoter ratio of 0.2:1, which is far from the range recited in the present claims. Consequently, there is nothing in the teachings of Pettersson et al. that would make a person skilled in the art believe that the claimed selected Mn:promoter range of from 2:1 to 3:1 is superior compared to other Mn:promoter ratios.

In addition, Thomsen does not remedy the serious deficiencies of Pettersson et al. Specifically, similar to Pettersson et al., Thomsen does not teach or suggest the Mn:promoter ratio recited in the present claims.

In conclusion, the results displayed in Tables 2a, 2b and 3 of the present specification demonstrate the surprising advantageous properties of the claimed Mn:promoter range of from 2:1 to 3:1, particularly in light of the fact that even relatively small increases in Liver Mean Mn contents are extremely important in MRI diagnostics.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited. In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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